Psychosis and the level of mood incongruence in Bipolar Disorder are related to genetic liability for Schizophrenia

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Key Points

Question: what is the relationship between polygenic liability for schizophrenia and the occurrence and level of mood-incongruent psychotic symptoms in bipolar disorder (BD).

Findings: in this case-control study which included 4436 BD and 4976 schizophrenia cases compared with 9012 controls, there was a gradient of schizophrenia polygenic risk scores effects: Schizophrenia > BD with prominent mood-incongruent psychotic features > BD with prominent mood-congruent psychotic features > BD with no psychosis all differential associations were statistically-significant.

Meaning: A gradient of schizophrenia liability, across schizophrenia and bipolar disorder, indexed by the occurrence and level of mood-incongruent psychotic symptoms has been shown for the first time

Abstract

Importance

Bipolar disorder overlaps with schizophrenia in both its clinical presentation and genetic liability. Alternative approaches to patient stratification beyond the current diagnostic categories are needed to understand the underlying disease processes/mechanisms, and develop new therapeutic interventions.

Objectives

To investigate the relationship between common-variant polygenic liability for schizophrenia, as indexed by polygenic risk scores (PRS) and psychotic presentations of bipolar disorder, using clinical descriptions which consider both the occurrence and the level of mood-incongruence of the psychotic symptoms experienced.

Design

Case control design: using multinomial logistic regression, to estimate differential associations of the schizophrenia liability across categories of cases and controls.

Settings & Participants

4436 bipolar disorder cases from the UK Bipolar Disorder Research Network, assessed using a unified interview protocol during the period 2000 - 2013. For comparison we included data from the large CLOZUK study of schizophrenia including 4976 treatment resistant schizophrenia cases and UK controls from the Type-1 diabetes genetics consortium (N=2,532) and a subsample of Generation Scotland (N=6,480).

Exposure

Standardised Polygenic Risk Scores (PRS) for schizophrenia were generated, using alleles with an association p-value < 0.05 in the second Psychiatric Genomics

Consortium genome-wide association study of schizophrenia, adjusted for the first 10 population principal components and genotyping-platform.

Main outcome measure

Multinomial logistic regression was used to model the associations of PRS with Bipolar disorder cases stratified by (1) RDC bipolar disorder subtypes (2) Lifetime-ever occurrence of positive and/or disorganised psychotic symptoms (3) Lifetime mood-incongruent psychotic features and (4) ordinal logistic regression modelling the association with mood-incongruence measured on an ordinal scale. Ratings were derived from the Schedule for Clinical Assessment in Neuropsychiatry interview (SCAN), the Operational Criteria checklist (OPCRIT) and the Bipolar Affective Disorder Dimension Scale (BADDS).

Results

PRS discriminated CLOZUK cases from controls, with each standard deviation increase in PRS almost doubling the relative risk ratio (RR) (RR=1.94, corrected p-value <0.0001, (95% C.I. 1.86, 2.01)). Across phenotypes, there was a gradient of effect with the strongest PRS association in CLOZUK, then RDC schizoaffective bipolar disorder (RR=1.37, corrected p-value <0.0001, (95% C.I. 1.22, 1.54)), RDC bipolar disorder subtype I (RR= 1.30, corrected p-value <0.0001, (95% C.I. 1.24, 1.36)) and RDC bipolar disorder subtype II (RR=1.04, p-value 0.258, (95% C.I. 0.97, 1.11)). Within BD cases, there was a gradient of PRS effect, indexed by the nature of psychosis, with the prominence of mood-incongruent psychotic features having the strongest association (RR=1.46, corrected p-value <0.0001, (95% C.I. 1.36, 1.57)), followed by BD with prominence of mood-congruent psychotic features (RR= 1.24, corrected p-value

<0.0001, (95% C.I. 1.17, 1.33)) and lastly, BD cases with no lifetime occurrence of psychosis (RR=1.09, corrected p-value =0.004, (95% C.I. 1.04, 1.15)).

Conclusion

We show for the first time a gradient of schizophrenia risk allele burden, across schizophrenia and bipolar disorder, indexed by the occurrence and level of mood-incongruent positive and disorganised psychotic symptoms.

Introduction

Although currently classified as a discrete diagnostic category [1-3], bipolar disorder (BD) overlaps considerably with schizophrenia (SCZ) in both its clinical presentation [4-13] and genetic liability [14-22]. BD is a phenomenologically heterogeneous construct and within the diagnostic category individuals may have quite different symptom profiles. It has been proposed, this manifest clinical heterogeneity is indicative of an underlying aetiological and pathophysiological heterogeneity and the degree of clinical similarity between BD and SCZ, reflects overlapping risk alleles which selectively influence specific, shared clinical characteristics, rather than the global risk for the disorders [23-25].

Delusions and hallucinations are common in BD [26, 27] with around one third of all psychotic features judged to be mood-incongruent [28, 29] that is, they are not readily understandable in the context of the person's mood state. Mood-incongruent psychotic features are associated with poorer prognosis, poor lithium-response and are qualitatively similar to the prototypic symptoms of SCZ [30-32], suggesting the hypothesis that BD psychosis and in particular individuals with mood-incongruent psychotic features, specify a subgroup/stratum with stronger aetiological links to SCZ. Stratified linkage and candidate gene studies of BD associations with chromosomal regions and genes implicated in SCZ show stronger effects in psychosis and mood-incongruent subsamples [33-36] and provide some support for this causal heterogeneity hypothesis, however as there is a lack of consistency in earlier linkage and candidate gene studies the overall support is weak.

Recently, meta-analysis of genome wide association studies (GWAS) have found a substantial polygenic component to both BD and SCZ risk, with a large amount (~30%) of their genetic variance explained by common risk alleles, partially shared across the

two disorders [20]. The polygenic risk burden can be calculated for individuals with a single summary measure, known as a polygenic risk score (PRS). As GWAS studies have become increasingly more powerful; PRS capture more polygenic risk. The ability to estimate the polygenic risk burden for individuals lets us examine the genetic basis of symptom domains, within and across the 2 disorders [37-39] in a more systematic way and with greater power than the historical linkage and candidate gene approaches. PRS-SCZ (imperfectly) differentiates cases of BD from controls [20, 40] and there are differential associations across subtypes of BD, with schizoaffective bipolar disorder (SABD) (a transitional or intermediate subtype characterised by an admixture of SCZ and BD symptoms) having a relatively larger burden of SCZ risk, compared to other BD subtypes [15, 41]. To date, lack of power in well phenotyped samples has hindered a fine scale examination of the relationship between SCZ risk and psychotic symptoms in BD.

We aimed to examine the relationship between polygenic liability for SCZ and psychotic presentations of BD using PRS generated from the most powerful SCZ-GWAS discovery set currently available [21]. Measures relevant to the occurrence and nature of psychotic symptoms were considered. We hypothesised BD with psychosis would be associated with higher polygenic risk for SCZ and that this association would be stronger when mood-incongruent psychotic features were present, given their phenotypic similarity to the psychotic symptoms of prototypic SCZ.

Methods

Sample Ascertainment

Bipolar Disorder sample

4436 unrelated cases of BD with deep phenotypic information, of European ancestry, domicile in the UK, and collected during the period 2000 - 2013 were available via the

UK Bipolar Disorder Research Network (www.BDRN.org) using recruitment methods which are reported in detail elsewhere [15, 42, 43]. The sample has 1399 cases not included in prior BDRN publications [15, 41]. All participants were assessed using a consistent interview protocol which included the semi-structured Schedule for Clinical Assessment in Neuropsychiatry interview (SCAN) [44] administered by trained research psychologists and psychiatrists, with very good to excellent inter-rater reliability for all domains of psychopathology [45]. Using information from both the SCAN interview and medical case note review, the Operational Criteria Checklist ratings was completed (OPCRIT) [46]. Research Diagnostic Criteria (RDC) [3]diagnoses, which differentiate individuals on the basis of the their pattern of mood and psychotic symptoms better [41] than either DSM [2] or ICD–10 [1], were made using the consensus lifetime best estimate method, informed by all sources of available information[47].

Schizophrenia sample

To allow comparison of BD with SCZ, we included a subset (N=4976) of the CLOZUK sample, which was anonymously collected via the Zapronex ® Treatment Access System (ZTAS) as detailed in a previous report [48]. All individuals were prescribed clozapine for Treatment Resistant SCZ (TRS) and are independent of, and unrelated (pi-hat <0.2) to individuals in the discovery GWAS of the PGC [21] which we used to derive effect size weighted risk alleles in this study. In principle, TRS samples might have a particularly high risk burden, but previous studies show PRS in CLOZUK are similar to other SCZ samples used by the Psychiatric Genomics Consortium[21].

Control Samples

The controls came from two UK sources: the Type-1 diabetes genetics consortium (TIDGC) (n = 2,532) are unscreened controls, recruited through the 1958 birth cohort

and used by the Type 1 Diabetes Genetics Consortium [49] and the other is a subsample of the Generation Scotland (n = 6,480) study, screened for psychiatric disorders [50]. Controls were genotyped on illumina® arrays which have high probe overlap with the genotyping platforms used in the BD and CLOZUK, are unrelated (pi-hat < 0.2) to individuals in the PGC-SCZ discovery set, and are well matched ancestrally to our case datasets [48].

All samples had appropriate ethics approvals.

Genotyping, quality control (QC), phasing and imputation

Bipolar cases

Genotypic data for the BD cases were processed in 3 batches, each on a different platform. To mitigate against potential bias from batch effects [51], stringent QC was performed on each platform separately prior to merging. Single nucleotide polymorphisms (SNPs) were excluded if the call rate was < 98%, minor allele frequency (MAF) was < 0.01 or they deviated from Hardy Weinberg equilibrium (HWE) at $p < 1x10^{-6}$. Individuals were excluded if they had minimal or excessive autosomal homozygosity (|F|>0.1), high pairwise relatedness (pi-hat > 0.2) or mismatch between recorded and genotypic sex. Following QC, the data for each platform were phased using SHAPEIT [52] and imputed with IMPUTE2 [53], using the 1000 Genomes panel (Phase3, 2014) as the reference. Imputed data were converted into the most probable genotypes (probability >0.9) and merged on shared SNPs. 4399 BD cases remained after QC.

CLOZUK cases and Controls

The CLOZUK and control samples had been though strict QC separately, before being phased and imputed simultaneously as part of a larger SCZ study [48].

After excluding SNPs with stand ambiguity; BD, CLOZUK and the control samples were merged and the imputed markers underwent a second QC filter [51], excluding SNPs that were missing in >5% of individuals, had imputation information score (INFO) <0.8, deviated from HWE at $p < 1x10^{-6}$ or had MAF <0.01. We excluded SNPs from the extended MHC (chr 6: positions 25-35 MB), given its extensive LD that is difficult to fully account for given its extensive LD.

Principal Component Analysis

To adjust for potential confounding from population structure, we performed PCA using PLINK v1.9, after LD pruning and frequency filtering the SNPs from the merged sample, keeping the eigenvectors for the first 10 principal components (PCs) to use as covariates in the association analysis.

Polygenic Risk Scores (PRS)

Using the 2014 PGC-SCZ meta-analysis as our discovery set [21], we calculated PRS for all individuals in our merged sample, as the sum of the risk alleles they carry, weighted by their effect size (logarithm of the odds ratio (OR)) in the discovery GWAS [20]. SNPs were LD pruned using p-value informed clumping, at r^2 <0.2 with 1MB windows. Risk alleles were defined as those associated with the PGC-SCZ study at p-value < 0.05, which at the current discovery sample size, captures SCZ liability maximally [21].

Outcome measure of lifetime psychosis & mood incongruence

Subtypes of BD

RDC subtypes were used as categorical outcomes in case control analyses. The RDC [3] and Diagnostic and Statistical Manual of Mental Disorders (DSM) [2], though not the ICD-10 Classification of Mental and Behavioural Disorder (ICD-10) [54], subdivides BD into bipolar I disorder (BD I) and bipolar II disorder (BD II) depending on the nature of the

mood states; mania in (BP I) and hypomania in (BP II). Additionally, all classification systems recognise an intermediate diagnosis, SABD, conceived to categorically capture presentations with an admixture of SCZ and BD symptoms. Psychotic symptoms are most prominent in SABD, then BD I, and least prominent in BD II [55, 56].

The Bipolar Affective Disorder Dimension Scale

The Bipolar Affective Disorder Scale (BADDS) [57] is based on 4 symptom domains [57] measuring the frequency and severity of Mania (M), Depression (D), Psychosis (P) and mood incongruence (I). Outcome measures were generated from the (P) and (I) subscale as follows:

1) A binary categorical outcome measure for lifetime occurrence of psychosis defined as an unambiguous episode of positive and/or disorganised psychotic symptoms, generated by dichotomising the BADDS psychosis (P) domain scale at a score > 9 [57].

2) A binary categorical outcome measure for lifetime occurrence of predominant mood-incongruent psychotic features (high v low prominence of mood-incongruence), defined as >19 on the incongruence scale (I) of the BADDS.

3) We also used an ordinal measure of mood-incongruent psychotic features which assesses the overall balance between mood-congruent and mood-incongruent psychosis across the lifetime, rated using all available information according to BDRN protocol (E supplement : Note 1)

Statistical Analysis

A multinomial logit model was used to estimate differential associations of standardised PRS, adjusted for the first 10 PCs and genotyping-platform, across categories of cases and controls. We report the estimated coefficients transformed to relative risk ratios (RR), defined as the exponentiated (B), where B is the regression coefficient estimate.

As there is a degree of arbitrariness about our binary classification low/high mood-incongruity, we also looked at PRS associations across levels of mood-incongruent psychotic features, using ordinal logistic regression. To examine whether SABD subtypes were driving the observed PRS association with mood-incongruent psychotic features, we did a sensitivity analysis excluding SABD cases. Post-estimation predicted probabilities were plotted to aid interpretation of the PRS associations across RDC subtypes of BD [58]. We performed 4 major analyses as defined above; to correct for multiple comparisons of PRS associations across different phenotypic strata within each model, bootstrapped standard errors and 95% confidence intervals were generated, as an approximation to exact permutation methods [59](supplementary E - Note 2) . Possible family-wise type-1 error proliferation was controlled for using the Bonferroni method, calculated by multiplying the bootstrapped p-values by four (the total number of independent analyses) [60], all reported p-values are corrected for both.

Post-hoc analyses using logistic regression compared the effect of PRS on lifetime occurrence of psychosis across BD I and BD II subtypes. We report odds ratios (OR) with 95% confidence intervals, uncorrected for multiple testing. To examine the distribution of RDC defined cases across levels of PRS, we converted the PRS to deciles and generated a stacked bar chart (SCZ (CLOZUK),SABD, BD I, BD II) , by decile.

Analyses were performed using PLINK v1.9 [61] or STATA (*Stata Statistical Software: Release 14*. College Station, TX: Stata Corp, LP).

Results

Sample description, Genotyping and quality control

After quality control procedures, 18,387 cases and controls (E-supplementary Table 1) with 3,451,354 imputed SNPs with INFO score > 0.8 and MAF >1% were available for analysis. Within the BD sample 52% (N = 2296) of cases endorsed a lifetime occurrence of definite psychosis, with <1% missingness in this variable (N=25). Of the BD cases with definite psychosis, 43% (N= 981) were classed as having high lifetime mood incongruent psychotic features. There was a 9% (N=214) missingness rate for the mood incongruence variable within the BD cases with psychosis.

Case Control PRS associations

As expected (Table 1 Section A), PRS discriminated CLOZUK cases from controls, with each standard deviation increase in PRS almost doubling the relative-risk ratio. PRS in those with a diagnosis of SABD or BD I, but not BD II, were significantly higher than controls. There was a gradient of effect, with the strongest PRS association CLOZUK > SABD > BD I > BD II.

PRS associations within cases

PRS discriminated SCZ from all RDC BD subtypes (Table 2). Within BD cases, PRS discriminates BD II from both BD I and SABD (figure 1). The percentage of CLOZUK cases increased monotonically with increasing decile PRS, while the percentage of bipolar subtypes decreased (Figure 2).

PRS associations with psychotic BD

Compared with controls, the burden of SCZ risk alleles was higher in people with BD, regardless of whether they had a lifetime history of psychosis (Table 1, Section B, Figure

2). However, the burden of SCZ risk alleles, was significantly higher in BD cases with a lifetime history of definite psychosis, compare to those without such a history (Table 1, Section B, figure 3). Within BD cases, PRS discriminated those with and without lifetime ever psychosis (RR=1.25, 95% bootstrapped adjusted p-value < 0.0001, C.I. (1.16, 1.33)).

Post hoc analyses showed the association between PRS and psychosis was present in people with BD I (OR = 1.21, 95% C.I. 1.10, 1.32) but not statistically significant in BD II (OR = 0.98, 95% C.I. 0.80, 1.18).

PRS associations with mood-incongruent psychotic features

Within the BD sample, those with psychosis characterised by high mood-incongruence have a higher SCZ polygenic risk than controls, with a one standard deviation increase in PRS increasing the RR of being in the high mood-incongruence category by 46% (RR= 1.46, bootstrapped, 95% C.I. 1.36, 1.57) (Figure 3, Table 1 Section C). Although the association was significantly weaker than for the high mood-incongruent group, schizophrenia risk alleles were still enriched in those with low mood-incongruence compared with controls (RR= 1.24, bootstrapped 95% C.I. (1.17, 1.33). Sensitivity analysis excluding the SABD group from the analyses found comparable results (not presented). Finally, a within-BD-case, analysis measuring mood-incongruence on the ordinal scale shows the odds of having a higher PRS increases with higher levels of mood-incongruence (OR=1.17, (bootstrapped p-value < 0.0001, 95% C.I. 1.08 - 1.27)).

Discussion

Main Findings

Higher PRS-SCZ in people with BD [20, 62] is well established. Here, we replicate and extend this observation, demonstrating a gradient of PRS associations across SCZ and BD subtypes (CLOZUK > SABD > BD I > BD II). We also show BD cases with a history of psychosis carry a higher burden of SCZ risk alleles, compared to BD without psychosis. Furthermore, individuals with BD and psychosis characterised by prominently mood-incongruent psychotic features, carry the highest burden of schizophrenia risk alleles, supporting our hypothesis that mood-incongruence indexes phenotypic features linked to SCZ liability. We found a clear exposure-response gradient, with increasing PRS corresponding to BD presentations with psychotic symptoms and increasing mood-incongruence (mood-incongruent > mood-congruent > no psychosis).

Previously published work examining polygenic risk for SCZ across BD, stratified by psychosis, did not find significant discrimination [41, 63] although a trend was observed with the effect consistent with the findings presented here. The most likely explanations for the enhanced signal in the current analysis are: the PRS were constructed using risk alleles derived from a larger SCZ-GWAS discovery set which reduces measurement error and improved power from the larger BD sample [64]. This group has shown[41], PRS-SCZ significantly differentiate RDC-SABD from non-SABD BD subtypes, while finding no statistically significant differential between BD stratified by psychosis, suggesting it is the nature of the psychotic symptoms rather than their presence which indexed (at least in-part) the shared liability for SCZ. The current analysis supports this proposition that it is the nature of psychotic symptoms (level of mood-incongruence) rather than the presence of psychosis *per se* which is the more important indicator of a shared

biologically-valid, underlying dimensional trait and this is captured but with less precision by the diagnostic category SABD.

Implications

Our study supports the hypothesis that within BD, positive and disorganized psychotic symptoms, and in particular mood-incongruenct psychotic features, represent a dimensionally defined stratum with underpinning biological validity. These features are not only phenotypically similar to those observed in people with prototypal schizophrenia but also index a greater shared genetic aetiology with schizophrenia therefore are likely to share more pathophysiology [65]. It is notable that in those diagnosed with BD I with no history of psychosis, the association with schizophrenia liability was weaker but still on average higher than in the control group, while in BD II subsample there was no overlap with SCZ liability. We are not suggesting psychotic features are the best or only index of shared pathophysiology, but having established stronger genetic links between the risk for schizophrenia and bipolar disorder characterised by the occurrence of psychosis and level of mood-incongruence, we now have a basis to refine this signal. These findings represent a step towards the goal of reconceptualising phenotypic definitions using richer clinical signatures, measured across quantitative/qualitative domains including, symptom loadings and biomarker expression, outlined in the rationale for the Research Domain Criteria (RDoC) [66, 67] and the road map for mental health research (ROAMER) [68] projects. It is probable however a multidimensional stratification process will better harness the observed clinical heterogeneity and define more precise patient-strata/subgroups in closer alignment with the underlying pathophysiology [68-70]

Methodological considerations

The RDC diagnoses and lifetime psychosis ratings used in the current analyses are based on both a semi-structured SCAN interview and case-note review by expert raters, with good to excellent inter-rater reliability. This can be expected to minimise rates of missing data and the likelihood of phenotypic misclassification[71]. Our psychosis phenotypes are broadly defined and likely to represent imperfect measurements of a continuously distributed phenotype[72], imposing categorical constraints as we have done is likely to reduce power. We generated PRS using a single discovery set p-value threshold of < 0.05 and dealt with multiple comparisons, across different phenotypic categories/strata using bootstrap re-sampling approaches within each of our 4 independent analyses, adjusting for family-wise type-1 error proliferation using Bonferroni's correction. We have mitigated against potential confounding due to population stratification and potential batch effects across cases and controls, by partialling out the first 10 PCs and genotyping platforms from the PRS. However, we have not been able to include (unmeasured) environmental exposure variables in our models and it is possible residual confounding from gene-environment correlations are present. Finally, we have only examined the effect of common variants, as rare variants are not captured by current GWAS.

Conclusions

We show here for the first time a gradient of SCZ risk allele loadings across schizophrenia and bipolar disorder, indexed by the occurrence and level of mood-incongruence of positive and disorganised psychotic symptoms. This represents a small but important step towards precision medicine in psychiatry through biologically validated patient stratification.

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Table 1: Differential Association of PRS across variously defined BD strata (controls as comparator category)

	N (subsample)	RR	Bootstrapped p-value	Bonferroni Corrected p-value	Bootstrapped 95% confidence intervals
CLOZUK	4,976	1.94	<0.0001	<0.0001	1.86, 2.01
		A) Bipolar Disorder cases stratified by RDC defined subtypes			
SABD	356	1.37	<0.0001	<0.0001	1.22, 1.54
BD I	1,268	1.30	<0.0001	<0.0001	1.24. 1.36
BD II	2,775	1.04	0.258	0.258	0.97, 1.11
		B) Bipolar Disorder cases stratified by lifetime occurrence of psychosis			
No LEP	2,079	1.09	0.001	0.004	1.04, 1.15
LEP	2,296	1.36	<0.0001	<0.0001	1.29, 1.43
		C) Psychotic Bipolar Disorder cases stratified by level of mood incongruence			
Low LMI	1,126	1.24	<0.0001	<0.0001	1.17, 1.33
High LMI	981	1.46	<0.0001	<0.0001	1.36, 1.57

CLOZUK – Treatment resistant Schizophrenia, treated with clozapine, BD I - RDC bipolar disorder subtype I, BD II - RDC bipolar disorder type II, SABD-RDC bipolar schizoaffective disorder, LEP – lifetime ever occurrence of psychotic symptoms, LMI – lifetime pattern of low/high mood incongruent psychotic features RR – relative risk ratio PRS adjusted for 1st 10 PCs and genotyping platform

Table 2: PRS-SCZ associations among cases

	RR	Bootstrapped p-value	Bonferroni corrected p-value	Bootstrapped 95% C.I.
SABD compared to TRS	0.71	<0.0001	<0.0001	0.63, 0.80
BD I compared to TRS	0.67	<0.0001	<0.0001	0.64, 0.71
BD II compared to TRS	0.54	<0.0001	<0.0001	0.50, 0.57
SABD compared to BD II	1.32	<0.0001	0.0001	1.16, 1.50
BP I compared to BD II	1.25	<0.0001	<0.0001	1.16, 1.35
SABD compared to BD I	1.05	0.407	0.407	0.93, 1.18

TRS - treatment resistant schizophrenia, treated with clozapine, BDI - RDC bipolar disorder subtype I, BD II - RDC bipolar disorder type II, SABD-RDC bipolar schizoaffective disorder, RR – relative risk ratio PRS adjusted for 1st 10 PCs and genotyping platform 95% bootstrapped C.I. - 95% confidence intervals.

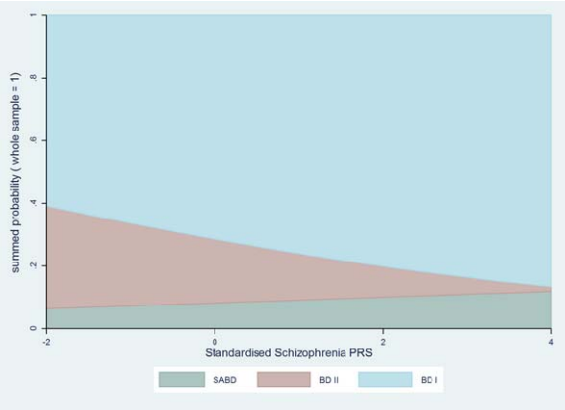

Figure 1: Probability of RDC bipolar subtype as a function of polygenic risk scores (PRS) for schizophrenia.
x-axis- standardized PRS in standard deviation units, SABD – schizoaffective bipolar type, BD I Bipolar Disorder type I , BD II – Bipolar disorder type II.

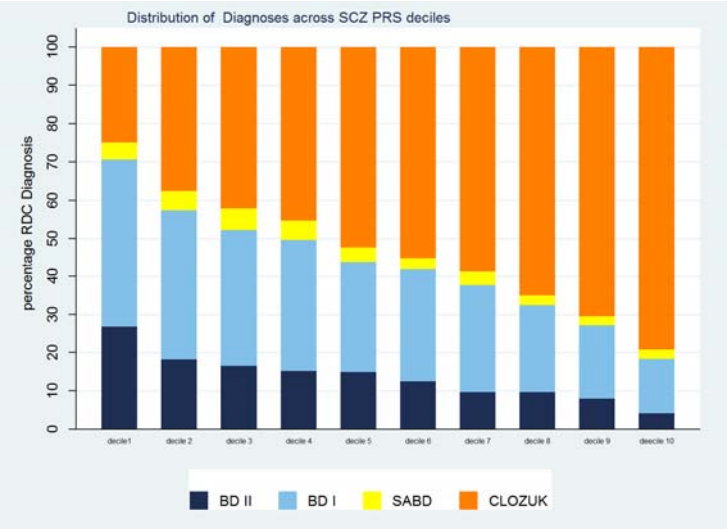

Figure 2: Percentage of RDC bipolar subtype as a function of polygenic risk scores (PRS) for schizophrenia grouped by decile.
x-axis- deciles of PRS, SABD – schizoaffective bipolar type, BD I Bipolar Disorder type I , BD II – Bipolar disorder type II.

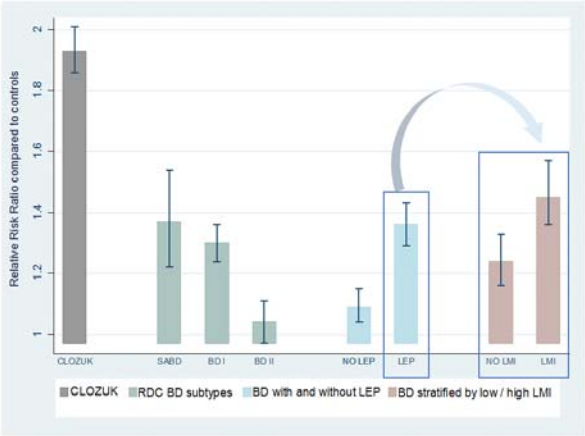

Figure 3: Relative Risk Ratios.

Height of bars represents Relative Risk Ratios for diagnosis or clinical feature compared with controls given 1 standard deviaton increase for schizophrenia polygenic score (PRS). Error Bars represent bootstrapped 95% confidence intervals. SABD – RDC schizoaffective bipolar type; , BD I – RDC bipolar disorder type I; BD II – RDC bipolar disorder type II: LEP – Lifetime Ever occurrence of psychosis within bipolar disorder; Low/High LMI – lifetime occurrence of Mood incongruence dichotomised as low or high within in those with psychotic forms of Bipolar Disorder.

Supplementary Notes

Note 1: Mood Congruence (Life-time)

Using all available information from SCAN interview and case not review the rater makes a judgement on the overall balance between mood-congruent and mood-incongruent psychosis across the lifetime with very good inter-rater reliability kappa = 0.89.

0	No psychotic features
1	Virtually all content congruent with affective state
2	More congruent than not
3	Congruent and incongruent equally
4	More incongruent than congruent
5	Virtually all content incongruent
9	Unsure/unknown

Note 2: Testing for multiple comparison using bootstrap resampling with replacement

Permutation methods, use existing data to create resampled data-sets, for example in logistic regression we shuffle the dichotomous outcome, to create many new simulated datasets. The justification for this reshuffling is that, this is what would be observed, if there was no association. This method guarantees a type 1 error control, under an exchangeability assumption [73] and this rationale extends to the bootstrap method used in this analyses, where we resample the observation vectors in memory intact, with replacement (so each observation could occur once, more than once or not at all – in a bootstrap replication sample of the same size as the original observed dataset) from the set of all observations instead of without replacement as in permutation based tests.

Using resampling with replacement allows us to maintain the strata and clusters within the variable structure of the MNLM, yet still approximating to permutation methods type 1 error control [74]. The variation across the replication samples, is used to estimate

the standard deviation/variance of the sampling distribution. We drew 5000 bootstrap samples for all the MNLM and OLM presented[75].

Results

Supplementary Table 1: Characteristics of study samples

Diagnostic Category	Sample Size	% Total Sample
RDC BD I	2,775	15.09
RDC BD II	1,268	6.90
RDC SABD	356	1.94
CLOZUK	4,976	27.06
CONTROLS	9,012	49.01
TOTAL	18,387	100